

MEMORANDUM



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research**

To: STN 125350-0

From: Sarah B. Tanksley, reviewer, CBER/OCBQ/DMPQ/MRB I

Through: Debbie Trout, consult reviewer, CBER/OCBQ/DMPQ/MRB I
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Subject: BLA review memo for IgPro20, CSL Bern, Switzerland

Action Due: February 28, 2010

Summary:

Human immunoglobulin product IgPro20 is manufactured at CSL Behring AG, located in Bern, Switzerland. The manufacturing process for gPro20 is identical to the manufacturing process of IgPro10, which was approved by FDA under BLA125201 in July of 2007, until the final manufacturing step. At this step IgPro20 is further concentrated into a 20% protein solution, whereas IgPro10 is concentrated to a 10% protein solution prior to final formulation. Figure 2 below was taken from the BLA and illustrates the manufacturing process for IgPro20. All steps are identical to IgPro10 manufacture until the -----(b)(4)-----, when the product is concentrated to a 20% protein solution using a -----(b)(4)----- process. CSL has requested a PMC to -----(b)(4)----- . The text of this PMC is found in the pertinent sections of this memo.

One (1) page determined to be non-releasable: (b)(4)

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The CSL Bern, Switzerland manufacturing site is licensed by FDA (US license No. 1766) for the manufacture and distribution of human plasma-derived medicinal products. Products manufactured in Bern are: Immune Globulin Intravenous (Human), liquid preparation; Immune Globulin Intravenous (Human), lyophilized preparation; Immune Globulin Intravenous (Human), liquid preparation; Albumin (Human); Immune Globulin (Human) anti-D; Immune Globulin (Human) anti-Cytomegalovirus.

Filling Line -(b)(4)- of the -(b)(4)- filling facility will be used to fill IgPro20. This is the same filling line used to fill IgPro10, and was inspected and licensed under STN125201-104 in March of 2009.

This review covers the steps in IgPro20 manufacture not previously licensed under IgPro10 (refer to Figure 2, CZS1600 to CZS2000). No changes were made to the facilities, utilities, equipment, environmental monitoring, visual inspection, or packaging and labeling systems. Changes were made to -----(b)(4)-----

-----, Product-contact equipment cleaning validations, a filling validation, and sterile filter validation were included and reviewed in this memo. The media fill report containing the container closure configuration for IgPro20 is also included and reviewed in this memo. Also, aspects of process validation under DMPQ purview are reviewed. The inspection was waived.

Review:

Facilities, Utilities, and Equipment

IgPro20 is manufactured at CSL Behring AG (Bern, Switzerland) from the ----(b)(4)---
-----, manufactured on site at the Bern facility, or
------(b)(4)-----, which is manufactured and shipped from -----(b)(4)-----
-----, All facilities used for the manufacture of IgPro20 are FDA licensed. IgPro20 and the FDA licensed human immunoglobulin product IgPro10 share the identical manufacturing process until the final manufacturing step. The intermediate manufacturers have made no changes to the facilities, utilities, or equipment in preparation for IgPro20 manufacture. All internal and external testing sites are already part of the CSL Behring AG product licenses. No new external testing sites are involved during the manufacture of IgPro20.

-(b)(4)- filling facility

IgPro20 is manufactured in the -(b)(4)- plant, which was licensed and inspected by FDA for the manufacture of IgPro10 in 2009 under STN125201/104. IgPro20 and IgPro10 share the identical manufacturing process until the final manufacturing step. At this step IgPro20 is further concentrated ------(b)(4)-----
----- process. The drug substance is initially ------(b)(4)-----, then the proline stabilizer is added. The material is further ----(b)(4)----- to 20%. The -(b)(4)-

-(b)(4)- filters are -----(b)(4)----- . A -(b)(4)- test is performed prior to the manufacture of every batch.

The -(b)(4)- is a dedicated production plant with dedicated equipment for the manufacture of the liquid immunoglobulin (Human) products IgPro10 and IgPro20. All product contact and production relevant equipment used for the manufacture of IgPro20 is identical with the qualified IgPro10 equipment. Qualification of the rooms, equipment, HVAC systems, utilities, and computer systems of the -(b)(4)- Production Plant were completed under the BLA for IgPro10. No changes to these systems were made. No changes to environmental monitoring procedures or excursion limits were made.

No new operational or performance qualifications of IgPro20-specific equipment were required. Appropriate cleaning validations using IgPro20 were performed and are discussed in the following section of this review. No changes to the utility systems, including HPW, WFI, pure steam, ethanol, and compressed air, were made for the implementation of IgPro20.

Additionally, no changes were implemented to the flows of waste, material, product, or personnel specific to IgPro20.

Bulk Process Validation

The manufacturing of IgPro10 and IgPro20 ----- (b)(4) ----- from ----- (b)(4) ----- is identical and has already been validated in connection with the manufacturing of IgPro10. Nevertheless, because the IgPro20 manufacturing procedure contains the complete process including the new, specific steps for bulk formulation (IgPro20-BLK, CZS1500 and CZS1550), the complete manufacturing process was evaluated in this process validation (steps CZ0100 to CZS1550). The process validation was performed at the -(b)(4)- plant at full scale, either with ----- (b)(4) ----- as starting material, October 2007 to April 2008.

The following lots were evaluated in the validation of IgPro20 bulk manufacturing are given in Table 1 below.

Table 1: Lots evaluated for validation of IgPro20 bulk manufacturing

Run #	Starting Material	Bulk Lot Number	Filling Lot Number	Start date	Origin of plasma
1	----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----	21 October 2007	US source
			----- (b)(4) -----		
2	--- (b)(4) --- -----	----- (b)(4) -----	----- (b)(4) -----	28 October 2007	US source
			----- (b)(4) -----		
3	----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----	30 October 2007	US recovered
			----- (b)(4) -----		

Process holding times are covered by the validation of the holding times of IgPro10. The maximal process run time is also covered by the validation of IgPro10 and is applied for IgPro20. According to the manufacturing procedure a final bulk may be stored for a maximum of -----(b)(4)----- . This hold time was validated with media for IgPro10 submission. For lot no. -----(b)(4)---- a bulk holding time of --(b)(4)- was applied as a worst case condition.

One deviation was under the purview of DMPQ:

Step -(b)(4)- (CZS1550): Integrity tests of -(b)(4)- filters after filtration; filters of all three lots passed at the latest in the third repetitions of the tests. According to procedure, -----(b)(4)-----.

----- (b)(4) -----

All acceptance criteria were met for the lots. Also, the -(b)(4)- filters of all three lots passed integrity tests at the latest in the third repetition of the tests. -----(b)(4)-----

-----.

The same Process Control Parameters (PCPs) were used in the process validation as in the validation for IgPro10. Quality Acceptance Tests (QATs) remain unchanged from IgPro10. The QATs for the formulation and filtration step under DMPQ purview are given below.

----- (b)(4) ----- [--(b)(4)--]

The final product control parameters were included in the process validation.

Table 3: End Product Parameter

End Product Parameter	Acceptance Criteria	Bulk Lot ----(b)(4)----		Bulk Lot ----(b)(4)----		Bulk Lot ----(b)(4)----	
		Filling Lot Lot -(b)(4)- -----	Filling Lot Lot -(b)(4)- -----	Filling Lot Lot -(b)(4)- -----	Filling Lot Lot -(b)(4)- -----	Filling Lot Lot -(b)(4)- -----	Filling Lot Lot -(b)(4)- -----
Pyrogen (US)	test passed	passed	passed	passed	passed	passed	passed

Pyrogen (EU)	test passed	passed	passed	passed	passed	passed	passed
Endotoxin	----(b)(4)----	-(b)(4)- -----	-(b)(4)- -----	-(b)(4)- -----	-(b)(4)- -----	-(b)(4)- -----	-(b)(4)- -----
Sterility	test passed	passed	passed	passed	passed	passed	passed

Filling Process Validation

The filling line was inspected by FDA and approved in March 2009 under PAS125201/104. Under this PAS, the bulk holding, sterile filtration, and aseptic filling in Filling Line -(b)(4)- was validated at full scale, using media fills. The maximum bulk hold times were validated with media holds in all vessels intended for the storage of IgPro20 (mobile bulk vessels -(b)(4)-). Six filling validation lots, derived from three bulk lots, were run, and were filled in 5 and 20 mL vials. The performed aseptic fillings cover also the filling into 10 mL and -(b)(4)- vials. See Table 4 below for the vial sizes and lots run.

Table 4: Filling Validation Lot Numbers and Vial Sizes

Validation Run #	Bulk Lot #	Filling Lot #	Vial Size	Date of filling
1	----(b)(4)----	----(b)(4)----	5ml	26 Sept 2008
		----(b)(4)----	20ml	23 Sept 2008
2	----(b)(4)----	----(b)(4)----	5ml	29 Sept 2008
		----(b)(4)----	20ml	30 Sept 2008
3	----(b)(4)----	----(b)(4)----	5ml	03 Oct 2008
		----(b)(4)----	20ml	02 Oct 2008

The IgPro20 bulk holding time of -(b)(4)- was required as worst case in at least one process validation run. Also, one of the mobile bulk vessels --(b)(4)-- was used, as these vessels are considered as worst case vessels for bulk holding of IgPro20.

The filling of a maximum amount of bulk solution and a maximum sterile filtration/filling time were not within the scope of this process validation since they are covered by the sterile filter validation and media fill.

------(b)(4)-----

Validation Performance

Process validation activities were performed from September 2008 to February 2009. General tests included predefining the batches, training, release of materials, equipment and systems settings, qualification status check, change control, worst case, batch finalization, stability studies, documentation, cleaning and sanitization. The critical process control parameters identified in the process risk analysis for bulk storage, sterile filtration and aseptic filling of IgPro20 were analyzed. No deviations concerning critical PCPs were observed.

Quality attributes for process validation were derived from the process risk analysis for bulk storage, sterile filtration and aseptic filling of IgPro20, the specifications for in-process controls (IPC) in aseptic filling of IgPro20, and specification for final product controls (FPC) of IgPro20.

----- (b)(4) ----- [(b)(4)]
----- (b)(4) -----

Final Product QATs under DMPQ purview include pyrogen, sterility, and endotoxin testing. The endotoxin specification for the final product is ----(b)(4)-----.

Container Closure

-(b)(4)-- glass injection vials (size designation -----(b)(4)-----), with -(b)(4)-
----- meeting the requirements for ----(b)(4)---- in accordance to -(b)(4)-
----- and the ----(b)(4)----
----- were chosen
for IgPro20. CSL has performed stability studies and container closure integrity through
----- (b)(4) ----- testing. A folding outer carton was chosen for the final market
presentation to protect IgPro20 from light and primary packaging from damages.

Table 6: Selected glass containers for IgPro20

Fill Size	Glass Container
1g (5ml)	----- (b)(4) ----- -----
2 g (10ml)	----- (b)(4) ----- -----
---(b)(4)---	----- (b)(4) ----- -----
4g (20mL)	----- (b)(4) ----- -----

The same stoppers are used for IgPro20 as are used for IgPro10 – they are ready-to-sterilize, -----(b)(4)-----, grey. A 20 mm crimp cap, made of -----(b)(4)---- with a rounded punched hole in the center protected by a -----(b)(4)---- plastic disc, is used.

Extractable and leachable studies were performed on the stopper. Typical antioxidants and curing agents were detected in extracts but no heavy metals and only low, non critical amounts of aluminum and zinc. No leachables were detected.

Table 7 summarizes the validated bottle and stopper combinations for IgPro20.

Table 7: Container and closures for IgPro20

Primary Packaging component
------(b)(4)-----
------(b)(4)-----
------(b)(4)-----
------(b)(4)-----
------(b)(4)-----
------(b)(4)-----
------(b)(4)-----

The BLA states that during routine manufacturing of IgPro20, the --(b)(4)-- container closure integrity test (---(b)(4)-- CCIT) is routinely performed on each process simulation run (media fill) carried out for the re-validation of the aseptic filling processes. The results from the last media fill using this configuration were in the BLA. The firm conducts media fills every --- (b)(4)---, and they will add the container closure system to the repertoire of those tested during the routine --(b)(4)-- media fills.

Table 8 below summarizes the data of the microbial CCITs performed during development with the primary packaging.

Table 8: ----(b)(4)--- container closure integrity tests (CCITs)

Test Item	Results			
Vial size	-(b)(4)-	-(b)(4)-	-(b)(4)-	-(b)(4)-
Number of filled vials	-(b)(4)- -(b)(4)- -(b)(4)-	-(b)(4)-	-(b)(4)-	-(b)(4)-
Lot No.	----(b)(4)---- ----(b)(4)---- ----(b)(4)----	----(b)(4)----	----(b)(4)----	----(b)(4)----
CCIT	No growth	No growth	No growth	No growth
Positive controls	growth	Growth	growth	growth

All performed sterility tests performed within the stability programs after the 12-month storage time have passed. Repetition of the sterility tests planned also at the end of the

----- (b)(4) -----

----- (b)(4) -----

----- (b)(4) -----

----- (b)(4) -----

----- (b)(4) -----

----- (b)(4) -----

----- (b)(4) -----

The firm contends that the initial ----- (b)(4) ----- test, the successful media fill, and the sterility results from the stability data demonstrate that their container closure is adequate. The firm was advised in a telecon that the ----- (b)(4) ----- test method is not adequate for this product, as the product is (b)(4) ----- . The data from the - (b)(4) - ----- validation demonstrates adequate container closure.

----- (b)(4) -----

----- (b)(4) -----

----- (b)(4) -----

Equipment Cleaning

The cleaning validations for IgPro10 are applicable for all upstream steps of IgPro20. This validation is limited to equipment used in process steps that are in contact with protein solution of higher protein concentration of IgPro20. The cleaning validation approach included -----(b)(4)-----

----- No bracketing with other potential residues than IgPro20 was applied. No grouping of equipment was applied. The cleaning validation of each equipment part of the formulation process sequence was performed three times.

The cleaning validation was performed concurrently to the manufacture of clinical lots of IgPro20. For automatically cleaned equipment, the minimum dirty holding time was -(b)(4)-. For manually cleaned equipment, the dirty hold time was -----(b)(4)-----
----- Equipment surfaces were visually inspected. Final rinse and swab samples were taken at the end of the cleaning process or following drying of the equipment, respectively. Final rinse samples were analyzed for -----(b)(4)----
----- Swab samples were analyzed for -(b)(4)-.

The following worst-case test conditions were applied:

----- (b)(4) -----

Equipment is either manually cleaned, or cleaned out of place. An overview of the equipment requiring cleaning validation for IgPro20 is listed below in Table 9.

(b)(4)-----

[--(b)(4)--]

Two (2) Pages Determined to be Non-Releasable: (b)(4)

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----- (b)(4) -----

Sterile Filtration

The same --(b)(4)-- sterile filter used in the IgPro10 manufacturing process is used for the manufacture of IgPro20. The filter validation was repeated using IgPro20, following the same approach as the corresponding --(b)(4)-- sterile filter validation submitted for the initial IgPro10 BLA. Validation was performed by the manufacturer according to the ----- (b)(4) ----- . Three filter lots were included within the testing, and IgPro20 was the test product fluid.

Filter validation included a ----- (b)(4) -----

----- . All procedures were described and results were given in the validation report. Criteria for validation were met and no deviations occurred.

Visual Inspection

CSL uses a manual visual inspection method for filled vials. No changes were made to the visual inspection system or method already licensed for IgPro10. Critical, major and minor defects remain unchanged. No new equipment or procedures were added. The last re-qualification report, dated February 2009, was included in the supplement. The report appears satisfactory.

Labeling and Packaging

No changes were made to the labeling and packaging facility. The latest re-qualification report, dated February 2009, was included in the submission.

Shipping Validation

No information on shipping of final product was included in the submission. Information was provided upon my request. Final product is shipped to CSL Behring, LLC, Bradley, IL. The same packaging configuration is used for IgPro10 as is intended for IgPro20. Shipping validation was approved under the IgPro10 BLA. The firm performed a risk assessment and determined that the shipping validation performed for IgPro10 is valid for IgPro20. All transports from CLS Behring AG, Berne (Switzerland) to CSL Behring LLC, Bradley IL for both of the finished products IgPro10 and IgPro20 are performed by the same type of road haulage, airfreight system, and packaging configuration. I found this acceptable.